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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,024	09/12/2005	Rene Bernards	BJS-620-378	8133

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,024	BERNARDS ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-10 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-10 and 13* is/are rejected.

7)☒ Claim(s) *5-10 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-16-07, 7-11-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 10-24-07.

Claims 5-10 and 13 are pending in the instant application.

Election/Restrictions

Claims 1-4, 11, 12 and 14-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10-24-07.

Applicant's election without traverse of Group II, original claim 5 (and amended claims 6-10 and 13) in the reply filed on 10-24-07 is acknowledged.

Claim Objections

Claims 5-10 and 13 are objected to because of the following informalities: Please provide the proper names for the acronyms recited in the claims ("HIF," "VHL" and "VDU"). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of screening for putative modulators of the ubiquitination and/or stability of HIF-α by determining the activity of a HIF-responsive reporter gene, or screening for modulators under conditions where VDU1 is capable of stabilizing HIF-α in the absence of a modulator. The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of genus comprising *HIF-responsive reporter genes*, nor do they describe the *conditions required for VDU1 which are capable of stabilizing HIF-α in the absence of a modulator.*

The specification teaches the in vitro inhibition of expression of independent family members of de-ubiquitinating enzymes (DUBs) using vectors expressing RNAi constructs (*a.k.a.* knockdown constructs), some of which were found to enhance TNF-α activation of NF-κB. The specification also teaches the potential use of an E2f-luciferase reporter and a Hypoxia Induced Factor 1-α (HIF-1 α) responsive promoter for testing the effect of knockdown constructs on cellular components involved in ubiquitination/de-ubiquitination processes.

The specification and claims, however, do not adequately teach a representative number of species for the genus comprising *HIF-responsive reporter genes*, nor do they

adequately teach the *conditions required for VDU1 stabilization of HIF-* α in the presence or absence of any modulators. Concise structural features or conditions that could distinguish structures within the genera comprising HIF-responsive reporter genes, or comprising the conditions required for VDU1 stabilization of HIF- α are missing from the disclosure, whereby a representative number of species of HIF-responsive reporter genes or whereby the conditions required for VDU1 stabilization of HIF-α are particularly described. For these reasons, the instant disclosure fails to provide adequate written description for the genera of *reporter genes* or of the *required conditions* claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (BBRC, Vol. 294, pages 700-709, 2002) and Li et al (J.Biol. chem.., Vol. 277, No. 7, pages 4656-4662, 2002), the combination further in view of Jones et al FASEB J., Vol. 16, pages 264-266, 2002).

The claims are drawn to methods to screen for modulators of VDU1 stabilization of HIF-α or the state of ubiquitination of HIF-α comprising contacting a test system in a cell with a candidate modulator, which test system comprises VDU1, HIF-α and further comprises VHL and optionally testing under hypoxic and normoxic conditions.

Li et al (BBRC, Vol. 294, pages 700-709, 2002) teach a ubiquitin ligase complex comprising VHL, VDU1 and/or VDU2, and the ubiquitination/de-ubiquitination of HIF-α. Li also teaches ubiquitination and an accompanying rapid degradation of substrate proteins in a VHL-dependent manner, as well as the de-ubiquitination of substrates by VDU proteins, both of which function as important regulatory steps in protein accumulation and turnover. Li teaches the ubiquitination and degradation of HIF-α under normoxic conditions, and an increase in HIF-α accumulation in the presence of mutated VHL, or under hypoxic conditions, which accumulation causes the development of highly vascularized tumors in VHL related diseases. Li teaches the motivation to study the role of VDU1 and VDU2 in de-ubiquitinating the ubiquitinated downstream targets of VHL, including HIF-α, and the role of VDU1 and VDU2 in regulating HIF accumulation and thereby regulating tumor progression. (see the abstract; text on p.

701, left col., text on page 703, bridging paragraph on pp. 705-706; text on page 706-708).

Li et al (J.Biol. Chem., Vol. 277, No. 7, pages 4656-4662, 2002) teach the ubiquitination and subsequent ubiquitin-proteasome degradation of VDU1 by VHL. Li teaches the potential role of VDU in regulating the ubiquitin-proteasome degradation pathway for protein degradation by de-ubiquitinating VHL. Li also teaches the regulation of protein turnover, via ubiquitination/ de-ubiqutination by VHL and VDU proteins, linking this with the regulation of HIF-α, and the relevance of HIF-α accumulation to tumorigenesis (see abstract and introductory text on pp. 4656-7; Results section, pp. 658, 4660, 4661; Discussion on p. 4662).

Li et al and Li et al do not teach the screening of modulators of VDU1 stabilization or ubiquitination state of HIF-α.

Jones et al (FASEB J., Vol. 16, pages 264-266, 2002) teach the role of NSAIDs in inhibiting angiogenesis by the ability of NSAIDs to inhibit hypoxia induced angiogenesis, by increasing expression of VHL, as well as teaching NSAIDs' inhibition of accumulation of HIF-α. Jones teaches a link between NSAIDs increasing VHL expression, thereby increasing ubiquitination and degradation of HIF-α, in turn inhibiting hypoxia induced VEGF/Flt expression, which then leads to the inhibition of angiogenesis (see entire text, which synopsizes the Prinicipal Findings and Conclusions).

It would have been obvious to one of ordinary skill in the art to screen for modulators of HIF-α stability and its ubiquitination state because the link between HIF

HIF-α accumulation and de-ubiquitination (or, conversely, between HIF-α degradation upon ubiquitination by VHL) was well known in the art and the accumulation of HIF during tumorigenesis was also well known in the art ,and so screening for modulators of HIF stability was a logical step whose motivation was taught previously by many in the art, including Li et al and Jones et al. One of ordinary skill in the art would have been motivated to screen for modulators of ubiquitination and of de-ubiquitination of HIF-α because high levels of HIF-α have been correlated with angiogenesis, which is required for rapid tumor growth and one would have motivated to inhibit tumorigenesis using a modulator of HIF accumulation.

It would have been obvious to screen for modulators of HIF-α stability/ubiquitination state in the presence of VDU (1 or 2) because VDU was known in the art to de-ubiquitinate HIF-α, leading to its degradation in the proteosome and detecting modulators of this process would help identify candidates for treating disorders involving improper HIF-α accumulation. It would have been obvious to screen for modulators of HIF stability/ubiquitination state in the presence of HIF-α, VHL and VDU because VHL and VDU were known in the art to ubiquitinate and de-ubiquitinate HIF-α, thereby participating in the regulation and fine-tuning of HIF accumulation, which affects angiogenesis, and modulators of this regulation can be identified for possible therapeutic agents in VHL and HIF related disease states, including various cancers.

One of ordinary skill in the art would have been motivated to screen for modulators in hypoxic and normoxic conditions because it was well known in the art that HIF accumulates under hypoxic conditions and screening under both sets of conditions would allow for the evaluation of candidate modulators which work effectively under various conditions, including at various stages of HIF accumulation, and at various stages of VHL related disease states.

For these reasons, the instant invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of

a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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1-2-08

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PRIMARY EXAMINER